PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

A Nationwide Study on the Risk of Autism After Prenatal Stress Exposure to Maternal Bereavement

Jiong Li, Mogens Vestergaard, Carsten Obel, Jakob Christensen, Dorthe Hansen Precht, Michael Lu and Jørn Olsen

Pediatrics 2009;123;1102
DOI: 10.1542/peds.2008-1734

ARTICLE

A Nationwide Study on the Risk of Autism After Prenatal Stress Exposure to Maternal Bereavement

Jiong Li, MD, PhD[a], Mogens Vestergaard, MD, PhD[b], Carsten Obel, MD, PhD[b], Jakob Christensen, MD, PhD[c], Dorthe Hansen Precht, MD, PhD[d], Michael Lu, MD[e], Jørn Olsen, MD, PhD[a,f]

[a]Department of Epidemiology, Danish Epidemiology Science Centre, and [b]Department of General Practice, Institute of Public Health, University of Aarhus, Aarhus, Denmark; [c]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; [d]Department of Pediatrics, Holbaek University Hospital, Region Zealand, Denmark; [e]Departments of Obstetrics and Gynecology and Community Health Sciences, Schools of Medicine and Public Health, and [f]Department of Epidemiology, School of Public Health, University of California, Los Angeles, California

The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Prenatal stress has been suggested to have a programming effect in brain development, and it has been linked to some neuropsychiatric disorders such as schizophrenia.

What This Study Adds

We found that prenatal stress exposure to maternal bereavement is not associated with an increased risk of autism in later life.

ABSTRACT

OBJECTIVE. Prenatal stress has been linked to several adverse neurobehavioral outcomes, which may share a common pathophysiology with autism. We aimed to examine whether prenatal stress exposure after maternal bereavement is associated with an increased risk of autism later in life.

METHODS. We conducted a nationwide population-based cohort study of all 1 492 709 singletons in Denmark born from 1978 to 2003. A total of 37 275 children were born to women who lost a close relative during pregnancy or up to 1 year before pregnancy. These children were included in the exposed group, and the remaining children were in the unexposed group. All children were followed up from birth until their death, migration, onset of autism, or the end of 2006. Information on autism was obtained from the Danish Psychiatric Central Register. We used Cox regression models to estimate hazard ratios in the exposed group compared with those in the unexposed group.

RESULTS. Maternal bereavement during the prenatal period was not associated with an increased risk of autism in the offspring. The hazard ratios did not differ by the nature of the exposure (maternal relationship to the deceased or cause of death). The hazard ratios were comparable between the 5 prenatal exposure periods under study (7–12 months before pregnancy, 0–6 months before pregnancy, first trimester, second trimester, and third trimester).

CONSLUSIONS. This is the first population-based cohort study to examine the effect of prenatal stress on autism in childhood. Our data do not support any strong association between prenatal stress after maternal bereavement and the risk of autism. *Pediatrics* 2009;123:1102–1107

www.pediatrics.org/cgi/doi/10.1542/peds.2008-1734

doi:10.1542/peds.2008-1734

Key Words
bereavement, prenatal, stress, autism, glucocorticoids, fetal programming

Abbreviations
CPR— civil personal registration
HR— hazard ratio
ICD—*International Classification of Diseases*
CI— confidence interval

Accepted for publication Aug 6, 2008

Address correspondence to Jiong Li, MD, PhD, Danish Epidemiology Science Centre, Department of Epidemiology, Institute of Public Health, University of Aarhus, Aarhus, Denmark. E-mail: jl@soci.au.dk.

AUTISM SPECTRUM DISORDERS are among the most common neuropsychiatric disorders in childhood with an estimated prevalence of 6 to 8 per 1000 individuals.[1–5] The disease has a high public health impact,[1,2] with up to 9 times higher health care expenditures in affected children compared with other children.[6,7] The etiology of autism is largely unknown,[8] but it is probably a complex developmental brain disorder with multiple genetic and environmental causes.[1,2] Several prenatal and perinatal factors have been shown to be associated with autism, suggesting that environmental factors operating in early life may play a causal role.[1,2]

Evidence from animal studies suggests that maternal stress during pregnancy may significantly affect the neurodevelopment of the fetus.[9,10] Fetal programming has often been cited as the underlying mechanism, which occurs when the normal pattern of fetal development is disrupted by an abnormal stimulus or insult at a critical time point.[9,11] Excessive glucocorticoids after stress in pregnant mothers could lead to dysfunction of the hypothalamo-pituitary-adrenocortical axis and have permanent effects on brain development.[9–12] In a number of epidemiologic studies, prenatal stress has been linked to congenital malformations,[13] social/emotional problems,[14,15] and psychiatric disorders including schizophrenia,[16,17] which may share a common pathophysiology with autism. However, little is known about the effect of prenatal stress on the risk of autism later in life.[18,19]

We aimed to examine the association between maternal bereavement during pregnancy and autism risk in

offspring. Bereavement occurs after a severe life event known to induce both short- and long-term stress.[20] We hypothesized that prenatal stress may affect the susceptibility of autism in a timing-specific and dose-response way.[18,19,21,22]

METHODS

We conducted a nationwide cohort study based on data from several national registers, including the Danish Civil Registration System,[23] Danish Medical Birth Register,[24] Danish Psychiatric Central Register,[25] and the Integrated Database for Longitudinal Labor Market Research.[26]

Study Population, Exposure, and Follow-up

We used data from the Danish Civil Registration System[23] to identify all singletons born in Denmark between January 1, 1978, and December 31, 2004, and their next of kin (mother, father, siblings, mother's siblings, and mother's parents). All live-born children and new residents in Denmark are assigned a unique civil personal registration (CPR) number, which is stored in the Danish Civil Registration System together with information on vital status, emigration, disappearance, address, and CPR numbers of family members. The CPR number is used as the key to individual information in all national registries.

We categorized children as exposed to stress in prenatal life if their mother lost a child, a spouse, sibling, or a parent during the pregnancy or up to 1 year before the pregnancy. The remaining children were included in the unexposed cohort. Cohort members were followed from birth until first diagnosis of autism, death, emigration, disappearance from the system, or December 31, 2006, whichever came first.

Autism

Information on autism for index children and mothers was obtained from the Danish Psychiatric Central Register,[25] which holds information on all admissions to Danish psychiatric inpatient facilities since 1969 and outpatient visits to psychiatric departments since 1995.[25] Diagnostic information was based on the Danish version of the *International Classification of Diseases, Eighth Revision* (ICD-8) from 1978 to 1993, and the *International Classification of Diseases, 10th Revision* (ICD-10) from 1994 onward. Autism cases were diagnosed after the first admission to a psychiatric hospital or in receipt of outpatient care because of autism (ICD-8 codes 299.00 and 299.01; ICD-10 codes F84.0 and F84.1).

Covariates

Perinatal factors (gestational age, birth weight, sibling order, Apgar score at 5 minutes) were retrieved from the Medical Birth Register.[24] The Medical Birth Register was established in 1968 and has been computerized since 1973. It holds data on all live births and stillbirths in Denmark, including characteristics of both mothers and newborns, and the variables with regard to pregnancy and delivery. Sociodemographic factors (paternal age, maternal age, residential place, maternal education, maternal income, and maternal cohabitation status) were obtained from the Integrated Database for Longitudinal Labor Market Research, which contains longitudinal information on demographic variables and socioeconomic data from 1980 onward.[26] Data on maternal psychiatric history (ICD-8 codes 290–299; ICD-10 codes F00–F99) was retrieved from the Central Psychiatric Register.[25]

Statistical Analysis

We used the Cox regression model (SAS 9.1 PROC PHREG procedure [SAS Institute, Inc, Cary, NC]) to estimate hazard ratios (HRs). The option of COVSANDWICH (AGGREGATE) was applied by using maternal CPR numbers as identification in the model to treat all siblings from the same mother as a matched set, to take into account common familial factors such as genetic predisposition and family environment. To examine whether the associations depended on type and timing of the death, we first categorized the exposed children from 2 groups of mothers: (1) mothers who lost a child or a spouse and (2) mothers who lost a parent or a sibling. We assumed that loss of a child or a spouse was more severe than loss of a parent or a sibling.[27] We further categorized the causes of death into 2 groups: (1) unexpected death (unexpected causes, ICD-8 codes 7950–7959 and ICD-10 codes R95–R97; motor vehicle accidents, ICD-8 codes 8100–8230 and ICD-10 codes V01–V89; suicide, ICD-8 codes 950–959 and ICD-10 codes: X60–X84; other accidents and violence, ICD-8 codes 800–807, 825–949, and 960–999 and ICD-10 codes V90–V99, W00–X59, and X85–Y89) and (2) death by other causes. The exposure window was divided into 5 periods (7–12 months before pregnancy, 0–6 months before pregnancy, first trimester, second trimester, and third trimester) to examine whether a potential effect of prenatal stress on autism differed across these periods.

We adjusted for the following factors that have been suggested to be potentially associated with both prenatal stress and autism[1,2]: gender (boys or girls), birth year (1978–1986, 1987–1995, or 1996+), gestational age (<37 or ≥37 weeks), Apgar score at 5 minutes (0–7, 8–9, 10, or unknown), sibling order (1, 2, 3, ≥4, or unknown), paternal age group (<29, 29–33, or ≥34 years), maternal age group (<27, 27–30, or ≥31 years), maternal residential area (capital city of Copenhagen area, cities with >100 000 inhabitants, or other places), maternal education (0–9, 10–11, or ≥12 years), maternal income (lowest quartile, second quartile, third quartile, or highest quartile in the calendar year), maternal cohabitation status (yes or no), maternal history of psychiatric diseases before birth of the child (yes or no). These paternal and maternal variables in the model were baseline characteristics at the birth year for the children.

The above-listed analyses also were performed in boys and girls, separately. We also restricted the above-listed analyses in the study subjects with a birth weight of >2500 g, gestational age of >37 weeks, and an Apgar score of 10.

TABLE 1 Baseline Characteristics of the Study Population

Variables	Exposed Cohort ($N = 37\ 275$), n (%)[a]	Unexposed Cohort ($N = 1\ 455\ 434$), n (%)
Gender		
Male	19 073 (51)	747 299 (51)
Female	18 202 (49)	708 135 (49)
Birth year		
1978–1987	5952 (16)	480 834 (33)
1988–1994	10 742 (29)	424 845 (29)
1995–2004	20 581 (55)	549 755 (38)
Sibling order		
1	8407 (23)	477 528 (33)
2	7733 (21)	374 851 (25)
3	3509 (9)	133 450 (9)
≥4	1230 (3)	46 435 (3)
Unknown	16 396 (44)	423 170 (29)
Gestational age		
<37 wk	1976 (5)	65 833 (5)
≥37 wk	35 299 (95)	1 389 590 (95)
Paternal age, y		
<28	11 170 (30)	461 855 (32)
29–33	13 616 (37)	514 601 (35)
>33	11 858 (32)	456 931 (31)
Unknown	631 (2)	22 047 (2)
Maternal psychiatric admission		
Yes	444 (1)	13 381 (1)
No	36 831 (99)	1 442 049 (99)
Maternal age, y		
13–26	12 099 (32)	506 852 (35)
27–30	12 180 (33)	458 488 (32)
>30	12 996 (35)	490 094 (34)
Maternal education		
Primary	14 694 (37)	583 807 (40)
Secondary	12 320 (31)	435 179 (30)
High	9607 (24)	348 002 (24)
Unknown	654 (2)	88 446 (6)
Maternal income		
First quartile	9715 (24)	339 886 (22)
Second quartile	15 507 (39)	535 275 (35)
Third quartile	8963 (22)	391 410 (26)
Fourth quartile	2435 (6)	100 398 (7)
Unknown	3247 (8)	147 153 (8)
Maternal cohabitation status		
Single	15 940 (43)	540 894 (37)
Cohabitation	20 681 (55)	826 094 (57)
Unknown	654 (2)	88 446 (6)
Maternal residence		
Copenhagen	8774 (24)	357 483 (25)
Cities[b]	4443 (12)	165 973 (11)
Other	23 404 (63)	843 532 (58)
Unknown	654 (2)	88 446 (6)

[a] We categorized children as exposed to stress in prenatal life if their mother lost a child, spouse, sibling, or parent during the pregnancy or up to 1 year before the pregnancy.
[b] Cities with >100 000 inhabitants.

TABLE 2 HRs for Autism in Children Whose Mothers Lost a Close Relative During Pregnancy or Up to 1 Year Before Pregnancy, According to Relationship to the Deceased or Cause of Death

	Cases/Sample Size	Crude HR	Adjusted HR (95% CI)
All death	68/37 275	1.39	1.00 (0.78–1.27)
Unexposed	2299/1 455 434	1.0 (Ref)	1.0 (Ref)
Death of a child/spouse	12/6721	1.04	1.03 (0.57–1.84)
Unexposed	2299/1 455 434	1.0 (Ref)	1.0 (Ref)
Death of a parent/sibling	56/30 683	1.48	0.98 (0.75–1.29)
Unexposed	1585/978 861	1.0 (Ref)	1.0 (Ref)
Death by unexpected causes	20/10 920	1.45	0.88 (0.56–1.36)
Death by other causes	48/26 355	1.37	1.05 (0.79–1.41)
Unexposed	2299/1 455 434	1.0 (Ref)	1.0 (Ref)

HRs were adjusted for gender, birth year, sibling order, gestational age, paternal age, maternal age, maternal psychiatric history, maternal education, maternal income, maternal residence, and maternal cohabitation status. Ref indicates reference group.

TABLE 3 HRs for Autism in Children Whose Mothers Lost a Close Relative During Pregnancy or Up to 1 Year Before Pregnancy, According to Timing of Exposure

Timing of Exposure	Cases/Sample Size	Crude HR	Adjusted HR (95% CI)
7–12 mo before conception	18/10 679	1.26	0.95 (0.59–1.52)
0–6 mo before pregnancy	19/12 188	1.14	0.88 (0.54–1.34)
Pregnancy period	31/14 408	1.70	1.15 (0.80–1.65)
First trimester	8/4198	1.49	1.00 (0.49–2.03)
Second trimester	13/5347	1.94	1.25 (0.72–2.17)
Third trimester	10/4863	1.63	1.17 (0.63–2.18)
Unexposed	2299/1 455 434	1.0 (Ref)	1.0 (Ref)

HRs were adjusted for gender, birth year, sibling order, gestational age, paternal age, maternal age, maternal psychiatric history, maternal education, maternal income, maternal residence, and maternal cohabitation status. Ref indicates reference group.

RESULTS

Of the 1 492 709 singleton children, 37 275 children were born to mothers who had experienced bereavement during pregnancy or up to 1 year before pregnancy, including 6 721 children of mothers who lost a child or spouse and 30 683 children of mothers who lost a parent or sibling. There were 86 591 (5%) who emigrated or disappeared at the end of follow-up. We identified 2367 (1.6 per 1000) children with a diagnosis of autism at the end of 2006.

The exposed and the unexposed cohorts were comparable on gender, gestational age, paternal age, and maternal characteristics (age, previous psychiatric illness, education, annual gross income, cohabitation status, and place of residence). Children in the exposed group tended to be born later in the study period and not to be the first child in the family (Table 1).

In the crude analyses, prenatal stress was associated with a 39% increased risk of autism, but the association disappeared (HR: 1.00 [95% confidence interval (CI): 0.81–1.31]) after adjusting for confounders, especially birth year. Similar results were obtained when analyses were stratified on exposure, defined by maternal relationship to the deceased (death of a child/spouse versus death of a parent/sibling) and cause of death (unexpected death versus other death) (Table 2).

Table 3 shows that the timing of the death did not modify the association between prenatal stress and autism

The incidence of autism in boys (2.5 per 1000) was fourfold of that in girls (0.6 per 1000). The HR was 1.03 (95% CI: 0.78–1.34) for boys and 0.85 (95% CI: 0.46–

1.55) for girls. When the analysis was restricted to those with a birth weight of >2500 g, a gestational age of >37 weeks, and an Apgar score of 10, the overall HR was 0.94 (95% CI: 0.71–1.24), which was similar to that for the whole study sample.

DISCUSSION

In this population-based cohort study, we found no support for our hypothesis. Severe stress after maternal bereavement during prenatal life did not increase the risk of autism in the offspring even when we took timing, nature, and severity of the exposure into account.

Few studies have examined the potential effect of prenatal stress on the development of autism. Beversdorf et al[18] showed that prenatal stressors were reported more frequently in autism cases than in controls. This finding was potentially subject to recall bias because study participants had to report life events almost 8 years back in time. Furthermore, the information on potential confounders was limited.[28] Recently, Kinney et al[19] found a dose-response–like pattern between severity of prenatal storm exposure and prevalence of autism, but the ecological study design allows for a variety of interpretations.

Compared with previous studies, our study had a number of important methodologic strengths. First, we followed a large population-based cohort of all children born in Denmark for up to 28 years with minimal loss to follow-up (<5%). Thus, the study was not biased by self-selection to the study or low compliance to follow-up, which has often been the problem in the follow-up studies. Second, previous studies in stress research were often limited by the lack of a standardized measure of stress, too little exposure contrast between the compared groups, or recall bias, which rendered difficulties in interpretation and comparison between studies. We believe bereavement is a good indicator of severe stress. A large body of literature has demonstrated bereavement to be one of the most stressful life events,[29,30] leading to a surge of stress hormones.[20,30–32] In our study, registration of day of death in the Danish Civil Registration System is valid and complete (close to 100%), making our exposure information accurate.[23] Third, previous empirical observations often failed to control for potential confounders and genetic background. We had detailed information on sociodemographic variables and maternal history of psychiatric disorders. Our crude analyses showed a 37% increased risk of autism in the exposed group; however, the difference between the exposed and unexposed groups decreased close to none after we adjusted for gender, birth year, neonatal characteristics (sibling order, Apgar score at 5 minutes, gestational age), maternal characteristics (psychiatric history, age, education, residence, income, cohabitation status), and paternal age. To adjust for these factors allowed us to disentangle the effect of both sociodemographic and perinatal factors as well as family history of psychiatric illnesses from the effect of prenatal stress.[33–41] It could be argued, however, that some of these variables (Apgar score, gestational age, etc) may be partial intermediate steps on the causal pathway from stress to autism,[33–41] and they should not have been included in the final model. Thus, we performed analyses confined to study participants with a gestational age of >37 weeks, birth weight of >2500 g, and an Apgar score of 10. However, results yielded were similar to those from the whole study sample.

It has been also suggested that the effect of prenatal stress on neurodevelopment varies according to the timing of exposure. Studies on schizophrenia[17] and congenital malformations[13] suggest that the first trimester is the most vulnerable period, but other studies on psychiatric admissions and experimental animal studies indicate that the time window of susceptibility is late in pregnancy.[16,42] Two recent studies related an increased autism risk to prenatal stress exposure in the middle or end of gestation,[18,19] although the timing in 1 of the studies was based on recall of the events that happened many years ago.[18] We did not observe such associations in any of the time periods. It has been shown that bereavement by unexpected causes might be more stressful than death by other causes,[13,21,22] and the death of a child is considered the most severe among all types of bereavement.[27,30,43] We observed no differences when we stratified for type of death (unexpected death versus other death, loss of a child/spouse versus other loss), which is not in line with the dose-response pattern in the observations of Kinney et al.[19] Autism is found more often in boys than in girls,[1,2] but no previous study has examined the gender differences in the effects of prenatal stress on autism. Evidence from animal studies has suggested that the sensitivity of developing brain areas to stress hormones is related to gender.[44] However, we observed similar results on the association between prenatal stress and autism in both genders.

One weakness of the study is that a gold standard diagnostic instrument for autism wasn't used. However, it has been shown that an autism diagnosis in the Danish Psychiatric Central Register has a high validity.[25,45] The validity of reported diagnoses of childhood autism was assessed in a small pilot sample of 40 children with infantile autism, and 37 (92%) met the criteria for a correct diagnosis based on a coding scheme developed by the Centers for Disease Control and Prevention.[45] Furthermore, we had no data on maternal lifestyle factors, which may confound the association.[1,2] However, harmful lifestyles achieved after bereavement may be on the causal pathway and should not be adjusted for. In addition, we do not have data on other prenatal or postnatal risk factors, such as maternal infection and intrapartum hypoxia,[1,2] but we do not expect these factors to be associated with prenatal bereavement.

CONCLUSIONS

Our study does not provide support a strong association between prenatal stress and the risk of autism in later life.

ACKNOWLEDGMENT

This study was supported by the Danish Medical Research Council (projects No. 271-05-0616 and 271-07-0437). Dr Li was also supported by NordFisk (project No. 070331) and Gigtforeningen (R54-A596-B286).

REFERENCES

1. Fombonne E. The epidemiology of autism: a review. *Psychol Med.* 1999;29(4):769–786
2. Newschaffer CJ, Croen LA, Daniels J, et al. The epidemiology of autism spectrum disorders. *Annu Rev Public Health.* 2007;28:235–258
3. Nicholas JS, Charles JM, Carpenter LA, King LB, Jenner W, Spratt EG. Prevalence and characteristics of children with autism-spectrum disorders. *Ann Epidemiol.* 2008;18(2):130–136
4. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators, Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—autism and developmental disabilities monitoring network, 14 sites, United States, 2002. *MMWR Surveill Summ.* 2007;56(1):12–28
5. Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of Autism in a US metropolitan area. *JAMA.* 2003;289(1):49–55
6. Mandell DS, Cao J, Ittenbach R, Pinto-Martin J. Medicaid expenditures for children with autistic spectrum disorders: 1994 to 1999. *J Autism Dev Disord.* 2006;36(4):475–485
7. Shimabukuro TT, Grosse SD, Rice C. Medical expenditures for children with an autism spectrum disorder in a privately insured population. *J Autism Dev Disord.* 2008;38(3):546–552
8. Hultman CM, Sparen P. Autism: prenatal insults or an epiphenomenon of a strongly genetic disorder? *Lancet.* 2004;364(9433):485–487
9. Viltart O, Vanbesien-Mailliot CC. Impact of prenatal stress on neuroendocrine programming. *ScientificWorldJournal.* 2007;7:1493–1537
10. Talge NM, Neal C, Glover V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry.* 2007;48(3–4):245–261
11. Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain. *J Neuroendocrinol.* 2001;13(2):113–128
12. Gitau R, Cameron A, Fisk NM, Glover V. Fetal exposure to maternal cortisol. *Lancet.* 1998;352(9129):707–708
13. Hansen D, Lou HC, Olsen J. Serious life events and congenital malformations: a national study with complete follow-up. *Lancet.* 2000;356(9233):875–880
14. Van den Bergh BR, Mulder EJ, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev.* 2005;29(2):237–258
15. O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry.* 2003;44(7):1025–1036
16. Huttunen MO, Niskanen P. Prenatal loss of father and psychiatric disorders. *Arch Gen Psychiatry.* 1978;35(4):429–431
17. Khashan AS, Abel KM, McNamee R, et al. Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. *Arch Gen Psychiatry.* 2008;65(2):146–152
18. Beversdorf DQ, Manning SE, Hillier A, et al. Timing of prenatal stressors and autism. *J Autism Dev Disord.* 2005;35(4):471–478
19. Kinney D, Miller A, Crowley D, Huang E, Gerber E. Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. *J Autism Dev Disord.* 2008;38(3):481–488
20. Rubin SS, Malkinson R. Parental response to child loss across the life cycle: clinical and research perspectives. In: Stroebe MS, Hansson RO, Stroebe W, eds. *Handbook of Bereavement Research: Consequences, Coping, and Care*. Washington DC: American Psychological Association; 2001:219–239
21. Li J, Laursen TM, Precht DH, Olsen J, Mortensen PB. Hospitalization for mental illness among parents after the death of a child. *N Engl J Med.* 2005;352(12):1190–1196
22. Li J, Precht DH, Mortensen PB, Olsen J. Mortality in parents after death of a child in Denmark: a nationwide follow-up study. *Lancet.* 2003;361(9355):363–367
23. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull.* 2006;53(4):441–449
24. Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull.* 1998;45(3):320–323
25. Munk-Jørgensen P, Mortensen PB. The Danish Psychiatric Central Register. *Dan Med Bull.* 1997;44(1):82–84
26. Denmark Statistics. IDA: an integrated database for labor market research [in Danish]. Available at: www.dst.dk. Accessed April 12, 2008
27. Skodol AE, Shrout PE. Use of DSM-III axis IV in clinical practice: rating etiologically significant stressors. *Am J Psychiatry.* 1989;146(1):61–66
28. McGinnis W. Could oxidative stress from psychosocial stress affect neurodevelopment in autism? *J Autism Dev Disord.* 2007;37(5):993–994
29. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. *J Psychosom Res.* 1967;11(2):213–218
30. Osterweis M, Solomon F, Green M. *Bereavement: Reactions, Consequences, and Care*. Washington DC: National Academy Press; 1984
31. Rubin SS. The death of a child is forever: the life course impact of child loss. In: Stroebe MS, Stroebe W, Hansson RO, eds. *Handbook of Bereavement*. New York, NY: Cambridge University Press; 1993:285–299
32. Moritz KM, Boon WM, Wintour EM. Glucocorticoid programming of adult disease. *Cell Tissue Res.* 2005;322(1):81–88
33. Mason-Brothers A, Ritvo ER, Pingree C, et al. The UCLA-University of Utah epidemiologic survey of autism: prenatal, perinatal, and postnatal factors. *Pediatrics.* 1990;86(4):514–519
34. Wilkerson DS, Volpe AG, Dean RS, Titus JB. Perinatal complications as predictors of infantile autism. *Int J Neurosci.* 2002;112(9):1085–1098
35. Deykin EY, MacMahon B. Pregnancy, delivery, and neonatal complications among autistic children. *Arch Pediatr Adolesc Med.* 1980;134(9):860–864
36. Zwaigenbaum L, Szatmari P, Jones MB, et al. Pregnancy and birth complications in autism and liability to the broader autism phenotype. *J Am Acad Child Adolesc Psychiatry.* 2002;41(5):572–579
37. Piven J, Simon J, Chase GA, et al. The etiology of autism: pre-, peri- and neonatal factors. *J Am Acad Child Adolesc Psychiatry.* 1993;32(6):1256–1263
38. Levy S, Zoltak B, Saelens T. A comparison of obstetrical records of autistic and nonautistic referrals for psychoeducational evaluations. *J Autism Dev Disord.* 1988;18(4):573–581
39. Bolton PF, Murphy M, Macdonald H, Whitlock B, Pickles A, Rutter M. Obstetric complications in autism: consequences or causes of the condition? *J Am Acad Child Adolesc Psychiatry.* 1997;36(2):272–281
40. Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. *Pediatrics.* 2001;107(4). Available at: www.pediatrics.org/cgi/content/full/107/4/e63

41. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. *Arch Gen Psychiatry.* 2004;61(6):618–627
42. Schneider ML, Roughton EC, Koehler AJ, Lubach GR. Growth and development following prenatal stress exposure in primates: an examination of ontogenetic vulnerability. *Child Development.* 1999;70(2):263–274
43. Levav I, Krasnoff L, Dohrenwend BS. Israeli PERI life event scale: ratings of events by a community sample. *Isr J Med Sci.* 1981;17(2–3):176–183
44. Weinstock M. Gender differences in the effects of prenatal stress on brain development and behaviour. *Neurochem Res.* 2007;32(10):1730–1740
45. Madsen KM, Hviid A, Vestergaard M, et al. A population-based study of measles, mumps, and rubella vaccination and autism. *N Engl J Med.* 2002;347(19):1477–1482

NEONATAL CEREBRAL INVESTIGATION

Editors: Rennie, Janet M; Hagmann, Cornelia F.; Robertson, Nicola J.
Publisher: Cambridge University Press
List Price: $190.00
Reviewer: Jay Goldsmith, MD (Tulane University School of Medicine)

Description: This is a comprehensive review of all types of cerebral imaging and electroencephalography set in the clinical context of evaluation of the newborn with neurologic abnormalities. Although other aspects of the neurologic evaluation are included, the book is principally concerned with aspects of brain imaging. This is an update of a book published in 1997 by Dr Rennie that was devoted entirely to neonatal ultrasound (Neonatal Cerebral Ultrasound (Cambridge University Press, 1997)).

Purpose: The purpose is to summarize the current knowledge and the authors' approach to the evaluation of neonatal neurologic abnormalities with an emphasis on the use and interpretation of brain imaging. These are certainly worthy objectives in this rapidly evolving field. Moreover, this British book is unique in that it is written from the perspective of the 3 neonatologist editors, rather than neurologists or neuroradiologists.

Audience: The intended audience includes any healthcare providers caring for high risk and sick newborn infants. It will be especially useful for neonatologists and neonatal fellows, pediatric neurologists, and neuroradiologists since the clinical-pathologic-radiologic correlations are so well done.

Features: A review of the principles of ultrasound, EEG, and magnetic resonance imaging begins the book, which then goes on to discuss the normal findings in these modalities. The rest of the book is devoted to neonatal clinical presentations, including the baby with seizures, depressed at birth, enlarging or large head, central nervous system malformations, and infection. An interesting final chapter covers postmortem imaging which may have medical-legal implications in this country. The imaging quality is superb and the figures are of the highest caliber. The diagnostic review of various problems often includes helpful tables and algorithms for the authors' academic approach to these issues. The absence of a neurologic or neuroradiologic editor does not appear to lessen the erudite quality of this excellent book.

Assessment: This is a wonderful book, done in the British style, reflecting the academic experience of senior neonatologists. This book fills a very important void in the field of neonatology and does so with a superb presentation.

A Nationwide Study on the Risk of Autism After Prenatal Stress Exposure to Maternal Bereavement

Jiong Li, Mogens Vestergaard, Carsten Obel, Jakob Christensen, Dorthe Hansen Precht, Michael Lu and Jørn Olsen

Pediatrics 2009;123;1102
DOI: 10.1542/peds.2008-1734